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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/594,387	06/15/00	MANOHARAN M	ISIS-4390

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EXAMINER	
SHIBUYA,M	
ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary	Application No. 09/594,387	Applicant(s) MANOHARAN
	Examiner MARK SHIBUYA	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 20, 2000* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 5-19, 21-29, 31, 32, 34-44, 46, and 48-57* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 5-19, 21-29, 31, 32, 34, 39-44, 46, 48, 53, and 55-57* is/are rejected.

7) ☒ Claim(s) *35-38, 49-52, and 54* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4 & 5*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Information Disclosure Statement

2. The information disclosure statement filed 2/10/2000, after the first action on the merits, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Copies of documents CK (Cohen, J.S. (ed), 1989), CL (Eckstein, F. (ed.), 1991), and CM (Green and Wuts, 1991) have not been provided by the applicants. The information disclosure statement has been placed in the application file, but the information referring to said documents CK, CL, and CM therein have not been considered.

3. The following U.S. Application Serial Numbers have been considered: 07/566,977, Reference JP, IDS filed 2/10/2000; and 08/465,880, JS, IDS filed 2/10/2000. The following U.S. Application Serial Numbers are unavailable to the examiner, have not been considered, and will be considered as they do become available: 07/463,358, Reference JO, IDS filed 2/10/2000; 08/383,666, Reference JQ, IDS filed 2/10/2000; 08/398,901, Reference JR, IDS filed 2/10/2000;

09/016,520, Reference JT, IDS filed 2/10/2000; 09/123,108, Reference JU, IDS filed 2/10/2000; and 09/130,973, Reference J, IDS filed 2/10/2000. The citations to the U.S. Application Serial Numbers on the PTO-1449 have been removed as failing to comply with 37 CFR 1.98, because citations must have publication dates pursuant to 37 CFR 1.98, but U.S. Applications, (unlike U.S. Patents), do not have publication dates.

Claim Objections

4. Claims 35-38, 49-52 and 54 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 35-38 and 49-52 are drawn to oligomeric compounds but depend from claims drawn to methods comprising arylproprionic acids. Claim 54 is drawn to methods wherein the protein is a cell surface integrin protein, but depends from claims drawn to methods comprising serum proteins, which are not cell surface integrins.

Double Patenting

5. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claims 1, 2, 5-19, 26-29, 32, 39-44, 46, 53, 55-57, are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-39 of copending Application No. 09/334,130. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Claims 1, 2, 5-19, 26-29, 32, 39-44, 46, 53, 55-57 of the instant application, are drawn to the genus of oligomeric compounds and oligonucleotides that are conjugated to an arylpropionic acid and that interact with a protein, and methods thereof; and so are obvious over the species of oligonucleotides covalently attached to an arylpropionic acid that interacts with a protein, and methods thereof, of claims 1-39 of copending Application No. 09/334,130.

Claim Rejections - 35 U.S.C. § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, 5-19, 21-29, 31, 32, 34-44, 46, 48-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of Written Description.

a. Claims 1, 2, 5-19, 21-29, 31, 32, 34-44, 46, 48-57 are drawn to oligomeric compounds conjugated to an arylpropionic acid that binds to a cellular protein, wherein the protein is a cellular protein or a serum protein that is alpha-1-glycoprotein, or a lipoprotein; and methods for increasing the binding of an oligonucleotide to a portion of the vascular system comprising "selecting an arylpropionic acid that is known to bind to a protein that resides, in part, in the circulating serum and in part in a non-circulating portion of the vascular system"; and methods for promoting cellular uptake of an oligonucleotide in a cell comprising selecting an arylpropionic acid that is known to bind to a protein that resides on the cellular membrane and extends, at least in part, on the external side of said membrane; for methods comprising serum proteins that bind oligonucleotides and arylproprionic acids at different sites; and methods comprising arylproprionic acids that bind to cell surface proteins, including integrins.

b. The specification at p. 14, line 24-p. 15, line 6, teaches that ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, and carprofen bind plasma proteins. The specification at p. 104-105, teaches that human alpha-1-acid glycoprotein is bound by drug moieties that include acenocoumarol, chlorpromazine, dipyridamole, imipramine, methadone, perphenazine, phenylbutazone, pindolol, progesterone, propanolol, RU 42633, RU 38486, thioridazine, ticlopidine, trifluoperazine, warfarin, and phenothiazines. The specification at p. 108, line 10-p.106, line 5, teach peptides that bind to cell surface integrins, and that Vitamin D, cortisol, sex hormones and thyroxine, bind to their respective binding proteins.

c. The specification as filed does not teach any particular arylpropionic acid that binds to a serum protein other than albumin, including alpha-1-glycoprotein, and does not teach any particular arylpropionic acid that binds to any particular cellular protein, or membrane protein, or "a protein that resides, in part, in the circulating serum and in part in a non-circulating portion of the vascular system". In fact, in regards to the last limitation, the specification does not disclose a particular example of "a protein that resides, in part, in the circulating serum and in part in a non-circulating portion of the vascular system". Furthermore, it is not disclosed as to whether this protein resides, in part, in the circulating serum or non-circulating portion of the vascular system, in a temporal sense, or a spatial sense or both. The specification does not disclose what is a "non-circulating portion of the vascular system". The specification as filed fails to provide written description for methods comprising serum proteins that bind oligonucleotides and arylpropionic acids at different sites; and methods comprising arylpropionic acids that bind to cell surface proteins, including integrins. The specification as filed fails to provide any written description at all for proteins or arylpropionic acids, other than those recited above, or what protein sequences or which arylpropionic acid molecular structures, are required to make and use in the invention as claimed. Therefore the specification as filed fails to provide written description for any proteins, other than serum albumin, that bind arylpropionic acids, particularly proteins that reside, "in part, in the circulating serum and in part in a non-circulating portion of the vascular system" and fails to provide any guidance on how the structures taught would have lead one to be in possession of compositions and methods comprising an arylpropionic acid that would bind to proteins other

than serum albumin. Thus, applicants disclosure combined with what was known in the art is not sufficient to describe the claimed genus of arylpropionic acids and proteins that they might bind, other than serum albumin, in such clear and concise and exact terms as to show applicants were in possession of the claimed invention.

9. Claims 1, 2, 5-19, 21-29, 31, 32, 34-44, 46, 48-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for arylpropionic acids that are ibuprofen and that bind to serum albumin, does not reasonably provide enablement for compositions comprising oligonucleotides covalently attached to any arylpropionic acid that binds to any protein other than serum albumin, including the cell surface protein integrin, and methods of delivery thereof; or for methods comprising serum proteins that bind oligonucleotides and arylpropionic acids at different sites; and methods comprising arylpropionic acids that bind to cell surface proteins, including integrins. The specification does not teach how to make an arylpropionic acid wherein the moieties R_1 and R_2 are simultaneously and independently C_1 to C_{12} alkyl groups (*i.e.*, no aryl group). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Claims 1, 2, 5-19, 21-29, 31, 32, 34-44, 46, 48-57 are drawn to compositions that comprise an oligonucleotide covalently linked to an arypropionic acid that interacts with a protein, and methods thereof, including interacting with a cell surface protein that is integrin, are not

enabled over the full scope of the claims, because of the unpredictability of the art and the specification's lack of particular guidance and particular direction.

b. The specification at pp. 7-8, discloses that ibuprofen, suprofen, pranoprofen, carprofen, fenbufen, ketoprofen, diazepam and other drugs bind at site II in subdomain IIIA of human serum albumin, while warfarin, phenyl butazone, dansylamide binds to site I.

c. The specification does not provide particular guidance or particular direction for arylpropionic acids that interact with protein other than serum albumin. The specification and the prior art disclose that the binding of ibuprofen is at a particular site, *i.e.*, site II in the albumin molecule. Thus binding is predicated upon the shape of the arylpropionic acid fitting into a pocket of the protein, as in a lock-and-key, as is commonly taught in the art of small molecule drug design. Indeed, some of the arylpropionic acids find use as nonsteroidal anti-inflammatory drugs (NSAID). It is clear that such an interaction is tailored upon the particular three dimensional structures of both the small molecule and the protein target. The claims, given their broadest reasonable scope, encompass any arylpropionic acid interacting with any protein, and are not commensurate with the disclosure as filed, which contemplates particular arylpropionic acids that are ibuprofen, suprofen, pranoprofen, carprofen, fenbufen, or ketoprofen, binding to a particular protein that is serum albumin. The specification as filed does not provide particular guidance or direction for other arylpropionic acids. The potential class of arylpropionic acids must be nearly as vast as the class of aryl compounds. The specification as filed does not provide particular guidance for the interaction of ibuprofen, suprofen, pranoprofen, carprofen, fenbufen,

or ketoprofen, much less any arylpropionic acid, with a protein other than serum albumin. The specification as filed does contemplate proteins other than serum albumin, such as alpha-1-glycoprotein or a lipoprotein or integrin, but does not disclose arylpropionic acids as binding to them. Given the specificity of the individual relationship between the arylpropionic acid and the protein that is required for binding, it is unpredictable that just any arylpropionic acid would fit, as a lock-and-key with a given protein.

d. Kleinberg et al., Am J Health-Syst Pharm (June 1995) vol. 52, pages 1323-1336, especially at p. 1325, teaches that a drug's moleuclar structure fits a particular type of receptor melecule and typically does not fit others, analogous to a lock-and-key relationship. Kleinberg et al., at p. 1326, teach that rational drug design depends upon the molecular structure, size and shape of potential drug compounds and the receptor molecules that are to be targeted. Herve et al., Clin. Pharmacokinet. 26 (1):44-58, 1994 (applicants' reference AU, IDS filed 8/3/00), at p. 46, name particular binding sites for specific binding by drugs on thye human serum albumin protein. McLure et al., Br J Clin Pharmacol, Feb. 2000, vol. 49, pages 453-461, especially at p. 454-456, found by equilibrium dialysis that naproxen, an arylpropionic acid that binds to serum albumin, did not bind to liver microsomal membrane preparations and McLure et al. teach that these microsomes comprised proteins.

e. Trial and error experimentation would be required of one of skill in the art to make compositions comprising an oligonucleotide covalently linked to any arylpropionic acid wherein said arylpropionic acid would interact with any protein other than serum albumin. The quantity of

experimentation required would include designing, synthesizing or using arylpropionic acids other than ibuprofen, suprofen, pranoprofen, carprofen, fenbufen, or ketoprofen, that would bind to and were demonstrated to bind to cellular, membrane, and vascular protein other than serum albumin. The specification does not teach how to make an arylpropionic acid wherein the moieties R_1 and R_2 are simultaneously and independently C_1 to C_{12} alkyl groups (*i.e.*, no aryl group). Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention.

Claim Rejections - 35 U.S.C. § 102

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 1, 2, 7-11, 14-19, 21, 26-28, 34, 39, 40, 41, 42, 55, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Hale et al., U.S. Patent No. 5,607,691, (applicant's reference, IDS filed 10/10/00).

a. Hale et al., U.S. Patent No. 5,607,691, (applicant's reference, IDS filed 10/10/00), at col. 2, lines 47-col. 4, line 67, col. 5, line 33-col. 6, line 9, col. 9, lines 32-49 and lines 55-66, col. 10, lines 9-11 and lines 17-25, co. 18, lines 11-67, col. 19, lines 1-col. 20, line 65, col. 23, lines 41-46, col. 25, lines 29-67, col. 27, line 52-col. 28, line 21, col. 37, line 1-col. 38, line 67, col. 39, lines 12-28 and lines 59-61, disclose oligonucleotides covalently attached to naproxen, which is an arylpropionic acid, as evidenced by Blaschke et al., Patent No. 4,973,745, (applicant's reference, IDS filed 10/10/00), and interacts with a serum or vascular protein, wherein the protein

is albumin, wherein the oligonucleotide includes a linking group attaching the drug to the oligonucleotide and inherently have a K_d lower than 20 μm with at least one serum protein, and wherein the oligonucleotide comprises internucleoside linkages that are phosphodiester, phosphorothioate and non-phosphorus containing linkages and a nucleoside that bears a 2'-substituent group; methods of increasing concentration of an oligonucleotide in serum comprising selecting the drug that binds to a serum protein for covalent attachment to the oligonucleotide and addition to serum, wherein the serum protein has a binding site for said drug moiety, wherein the serum protein has a binding site for the oligonucleotide, wherein said serum protein is thrombin, which has a binding site for said oligonucleotide that is an aptamer, and a distinct binding site for the drug; methods of increasing the capacity of serum for an oligonucleotide, and wherein the serum protein is albumin.

Claim Rejections - 35 U.S.C. § 103

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 1, 2, 7-11, 14-17, 21, 26-28, 34, 39, 40, 41, 55, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hale et al., U.S. Patent No. 5,607,691, (applicant's reference, IDS filed 10/10/00), and further in view of Blaschke et al. Patent No. 4,973,745, (applicant's reference, IDS filed 10/10/00), Herve et al., Clin. Pharmacokinet. 26 (1):44-58, 1994 (applicants' reference AU, IDS filed 8/3/00), Lagrange et al., Fundam. Clin. Pharmacol. 1998: 12: 286-291, and applicants' admission at page 14, line 21-p. 15, line 3 of the instant specification.

a. **Hale et al., U.S. Patent No. 5,607,691**, (applicant's reference, IDS filed 10/10/00), at col. 2, lines 47-col. 4, line 67, col. 5, line 33-col. 6, line 9, col. 9, lines 32-49 and lines 55-66, col. 10, lines 9-11 and lines 17-25, co. 18, lines 11-67, col. 19, lines 1-col. 20, line 65, col. 23, lines 41-46, col. 25, lines 29-67, col. 27, line 52-col. 28, line 21, col. 37, line 1-col. 38, line 67, col. 39, lines 12-28 and lines 59-61, disclose oligonucleotides covalently attached to naproxen, which is an arylpropionic acid, as evidenced by Blaschke et al., Patent No. 4,973,745 (applicant's reference, IDS filed 11/16/00), and interacts with a serum or vascular protein, wherein the protein is albumin, wherein the oligonucleotide includes a linking group attaching the drug to the oligonucleotide and inherently have a K_d lower than 20 μm with at least one serum protein, and wherein the oligonucleotide comprises internucleoside linkages that are phosphodiester, phosphorothioate and non-phosphorus containing linkages and a nucleoside that bears a 2'-substituent group; methods of increasing concentration of an oligonucleotide in serum comprising selecting the drug that binds to a serum protein for covalent attachment to the oligonucleotide and addition to serum, wherein the serum protein has a binding site for said drug moiety, wherein the serum protein has a binding site for the oligonucleotide, wherein said serum protein is thrombin, which has a binding site for said oligonucleotide that is an aptamer, and a distinct binding site for the drug; methods of increasing the capacity of serum for an oligonucleotide, and wherein the serum protein is albumin.

b. Hale et al. does not teach that naproxen is an arylpropionic acid, and does not teach other arylpropionic acids that are ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, or carprofen.

c. **Blaschke et al., Patent No. 4,973,745**, (applicant's reference, IDS filed 10/10/00), discloses that "[m]any 2-arylpropionic acids are applied in their racemic mixtures for rheuma therapy due to their analgeis and antipholgistic properties and Blaschke et al. contemplate using 2-arylpropionic acids that include flurbiprofen, fenoprofen, ketoprofen, naproxen, benoxaprofen and ibuprofen.

d. **Herve et al. (Clin. Pharmacokinet. 26 (1):44-58, 1994)(applicants' reference AU, IDS filed 8/3/00)**, at p. 50, teach that ibuprofen binds to plasma proteins.

e. **Lagrange et al., Fundam. Clin. Pharmacol. 1998: 12: 286-291**, at p. 286, teaches that the non-steroidal anti-inflammatory drug ketoprofen is extensively bound to serum albumin.

f. **Applicant's admission at page 14, line 24-p. 15, line 6 of the instant specification**, discloses that ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, and carprofen bind plasma proteins.

g. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have made and used an oligonucleotide covalently attached to a non-steroidal drug moiety that interacts with a protein, and methods thereof, wherein the drug moiety is aspirin, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, or carprofen.

h. One of ordinary skill in the art would have been motivated to make and use oligonucleotide covalently attached to a non-steroidal drug moiety that interacts with a serum protein, and methods thereof, wherein the drug moiety is an arylpropionic acid, such as ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, or carprofen (as taught by, *e.g.*, Blaschke et al.), because Hale et al., at col. 38, lines 46-67, disclose that functionality modifier capable of extending the excretion half-life of a pharmaceutical agent can comprise a moiety capable of binding to a serum protein, such as human serum albumin; and Herve et al., Lagrange et al., and the applicant's admission state that the aforementioned drugs will bind to serum proteins. Thus one of ordinary skill in the art would have been motivated to make and use the claimed oligonucleotide complexes and methods thereof, in order to increase the excretion half-life of pharmaceutical agents.

14. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hale et al., U.S. Patent No. 5,607,691, (applicant's reference, IDS filed 10/10/00), as applied to claims 1, 2, 5-11, 13-17, 20-23, 25-30, 33, 34, and 37-39 above, and further in view of Baker et al., U.S. Pat. No. 5,789,573.

a. Claims 18 and 19 are drawn to an oligomeric compound conjugated to a ligand that interacts with a protein wherein said ligand is a drug moiety that binds to the protein, wherein the oligomeric compound comprises a 2'-substituent group is O-alkylalkoxy and wherein the 2'-substituent group is methoxyethoxy.

b. Hale et al. does not disclose an oligomeric compound comprises a 2'-substituent group is O-alkylalkoxy and wherein the 2'-substituent group is methoxyethoxy.

c. **Baker et al., U.S. Pat. No. 5,789,573**, at col. 3, line 37-col. 4, line 30, discloses oligonucleotides that comprises a 2'-substituent group is O-alkylalkoxy and wherein the 2'-substituent group is methoxyethoxy, in order to increase the stability of oligonucleotides.

d. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have made and used an oligomeric compound conjugated to a ligand that interacts with a protein wherein said ligand is a drug moiety that binds to the protein, wherein the oligomeric compound comprises a 2'-substituent group is O-alkylalkoxy and wherein the 2'-substituent group is methoxyethoxy. One of ordinary skill in the art would have motivated to make and use oligomeric compounds that comprise a 2'-substituent group is O-alkylalkoxy and wherein the 2'-substituent group is methoxyethoxy in order to increase the stability of the oligonucleotide, as taught by Baker et al. Absent evidence to the contrary, one of ordinary skill in the art would have had a reasonable expectation of success in making and using oligomeric compounds comprising oligonucleotides that comprised a 2'-substituent group that was O-alkylalkoxy and wherein the 2'-substituent group was methoxyethoxy because the making and using of oligonucleotides with these 2' modification was well-known in the art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC),* whose telephone number is (703) 308-9355, and/or to the patent analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

16. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.

17. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technology Center 1600
October 1, 2001

ANDREW WANG
PRIMARY EXAMINER